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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,996	12/30/1999	JOHANNES CHRISTIANUS VAN GROENINGHEN	49477(1958)	3246

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/446,996	VAN GROENINGHEN, JOHANNES CHRISTIANUS	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Aditi Dutt.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 March 2008 has been entered.

Status of Claims

2. The amendment filed on 4 February 2008 has been entered into the record and has been fully considered.

3. Claims 14, 17 and 19 are amended. Claims 1-9 and 12 are canceled.

4. Claims 14-20, drawn to a method for decreasing cellular replication in a GnRH receptor positive tumor comprising administration to the subject a GnRH agonist, wherein the GnRH agonist is a GnRH analogue, are under consideration in the instant application. It is to be noted that claims 14-20 are examined in light

of Applicants' species election of GnRH agonists. The text of those sections of Title 34, U.S. Code, not included in this action can be found in a prior office action.

Response to Amendment

Withdrawn objections and/or rejections

5. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (4 February 2008).

6. Upon consideration of the amendment of claims 14 and 19 to narrow the limitation of tumor by reciting "malignant tumor" along with Applicant's persuasive argument, rejection of claims 14 and 19, under 35 U.S.C. 102(b), is withdrawn.

7. Upon consideration of the amendment of claims to narrow the limitation of tumor by reciting "malignant tumor", and the listing of specific analogues, the rejection of claims 14-20, under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn.

Claim objection

8. Claim 14 is objected to because of the following informalities:

The use of the trademarks for GnRH analogues has been noted in claim 14. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Appropriate correction is required.

New grounds of rejection

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 14, 16 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Labrie F (U.S. Patent No. 4,760,053, dated 26 July 1988).

11. Claims 14, 16 and 18 recite a method of decreasing cellular replication of a GnRH receptor positive tumor, such as malignant tumor of the brain, melanoma, comprising administration of a GnRH agonist or analogue selected from leuprorelin, buserelin, goserelin, etc., wherein the results show a decreased cellular replication of the tumor.

12. Labrie teaches a combination therapy of sex steroid dependent cancers such as skin cancer, brain cancer, etc. (col 3, lines 25-30, 45-46), comprising the administration of LHRH (luteinizing hormone releasing hormone - another name

for GnRH) agonist along with an antiandrogen, in individual compositions (claim 6 of the reference), and in amounts sufficient to inhibit tumor growth (col 5, lines 53-55; col 6, lines 45-48; col 11, lines 27-55; claims 1-2 of the reference). The reference further teaches that LHRH or GnRH agonists are synthetic analogs of the natural GnRH that include Leuprolide and Buserelin (col 8, lines 47-48; col 8-9; col 9, lines 47-48; col 2, lines 16-23). Furthermore, Labrie teaches that following the above treatment, the cancers are inhibited, thereby implying a decrease in the cellular replication of the tumors (col 15, lines 13-16). Because GnRH agonists are administered for the inhibition of tumor growth, the tumors inherently express GnRH receptors or are GnRH receptor positive tumors. Thus, Labrie clearly anticipates the claimed invention.

13 Claims 14-16 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Slusher et al, (US Patent No. 5,804,602, filed 17 June 1996).

14. Claims 14-16 and 18 recite a method of decreasing cellular replication of a GnRH receptor positive tumor, such as malignant tumor of the brain, melanoma, Kaposi sarcoma, Ewing sarcoma, neuroblastoma, etc., comprising administration of a GnRH agonist or analogue selected from Leuprorelin, Buserelin, Goserelin, etc., wherein the results show a decreased cellular replication of the tumor.

15. Slusher et al. teach the method for inhibiting cancer by administering a composition comprising Goserelin, Buserelin or Leuprolide as chemotherapeutic agents (col 14, lines 18-29; col 16, lines 51-54; col 18, lines 54-59; col 19, lines

4-6, 10; Table IV), along with the enzyme N-acetylated-α-linked acidic dipeptidase (NAALADASE) inhibitors, wherein the tumors to be treated include brain cancer, Ewing's sarcoma, Kaposi's sarcoma, melanoma, neuroblastoma, etc. (col 9, lines 13-15, 18, 21, 23, 26 and 29; Examples 22, 31, 36, 42, 45 and 52). Because GnRH agonists are administered for the inhibition of tumor growth, the tumors inherently express GnRH receptors or are GnRH receptor positive tumors. Thus Slusher et al. clearly anticipate the claimed invention.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Labrie F (U.S. Patent No. 4,760,053, dated 26 July 1988), or Slusher et al, (US Patent No. 5,804,602, filed 17 June 1996), in view of Nagy et al. (PNAS 93: 7269-7273, 1996).

19. Claims 14-20 recite a method of decreasing cellular replication of a GnRH receptor positive tumor, such as malignant tumor of the brain, Kaposi sarcoma, Ewing sarcoma, melanoma etc., comprising administration of a GnRH agonist or analogue selected from leuprorelin, buserelin, etc., with or without being combined or coupled with a cytotoxic substance, wherein the results show a decreased cellular replication of the tumor.

20. The teachings of Labrie or Slusher et al are set forth above.

21. Labrie or Slusher et al. do not teach that the GnRH agonists are coupled to, or are used in combination with a cytotoxic substance.

22. Nagy et al teach the administration of LH-RH agonist or analogs coupled to cytotoxic anticancer drugs Doxorubicin (DOX) or its several times more potent daunosamine modified derivative in animal tumor models, to target and inhibit tumors with the peptide (i.e. GnRH) receptors, thereby decreasing tumor growth (abstract, paragraph spanning pages 7272 and 7273).

23. It would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the inhibition of tumors comprising administration of GnRH agonists in a subject as taught by Labrie or Slusher et al., by administering GnRH agonists conjugated or coupled to

cytotoxic agents as taught by Nagy et al. The person of ordinary skill in the art would have been motivated to make that modification because the coupling results in providing the targeted chemotherapeutic molecules (or GnRH analogs plus the cytotoxic agent, e.g. DOX) to act on tumors expressing the LHRH receptors. Furthermore, the coupled cytotoxic LHRH analogs are less toxic and significantly more potent in inhibiting tumor growth, specifically in tissues with GnRH receptors (page 7272, last para). The person of ordinary skill in the art would have expected success because GnRH receptor positive tumors were being treated with GnRH analogs alone or in combination with cytotoxic chemotherapeutic chemicals at the time the invention was made.

24. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

Non-Statutory

25. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA

1969).

26. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

27. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

28. Claims 14-17 and 19, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35-40 and 54 of U.S. Patent Application number 10/327,621, dated 20 December 2002. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a method for decreasing cellular replication in a GnRH receptor positive tumor, such as malignant tumors of the brain including malignant glioma or Glioblastoma multiforme, and Kaposi sarcoma in a subject, comprising administering to the subject a GnRH agonist consisting of leuprorelin, buserelin, etc., alone or coupled to a cytotoxic substance, such that the cellular replication of the above GnRH receptor positive tumors is decreased.

29. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's Response

30. Applicant traverses the rejection, however, states that the terminal disclaimer will be filed at the time when no grounds of rejection will remain.

31. Applicant's argument is considered, but not found to be persuasive. Because other grounds of rejection remain, the double patenting rejection is maintained for reasons of record until the terminal disclaimer is filed.

Conclusion

32. No claims are allowed.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

34. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

35. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
14 June 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649